Hyperpolarized C-13

J. Stefan Petersson[1], Edvin Johansson[1], Peter Magnusson[1], Sven Månsson[2]
1 - GE Healthcare, Medeon, Malmö, Sweden
2 - Dept. of Experimental Research, Malmö University Hospital, Malmö, Sweden

Hyperpolarization vs. thermal equilibrium polarization

The signal to noise (*SNR*) value found in a MR imaging experiment may, assuming that the patient is the main noise source, be described according to:

$$SNR \sim \gamma c P \tag{1}$$

Where γ and c are the gyromagnetic ratio and the concentration of the nucleus, respectively. P, the polarization, describes the net magnetization per unit volume and thus the available signal. Nuclei with spin quantum number I = ½ (e.g. ^{1}H, ^{3}He, ^{13}C, ^{129}Xe) may orient themselves parallel or anti-parallel with respect the external main magnetic field. The polarization is defined by

$$P = \frac{N^+ - N^-}{N^+ + N^-} \tag{2}$$

Where N^+ is the number of spins parallel and N^- is the number of spins anti-parallel to the magnetic field. The N^+ will at thermal equilibrium be slightly higher populated than the N^- state and for a nucleus with I = ½ the polarization may be calculated using the expression:

$$P = \tanh\left(\frac{\gamma \hbar B_o}{2 k_B T}\right) \tag{3}$$

Where tanh is the hyperbolic tangens function, $\hbar$ the Planck constant, B_o is the main magnetic field strength, k_B the Boltzmann constant and T is the temperature. At a magnetic field of 1.5 T the polarization of the protons (^{1}H) at body temperature is only ~5 x 10^{-6} and for ^{13}C ~1.0 x 10^{-6}. The polarization is proportional to the magnetic field strength. Consequently, a 3 T scanner will result in a doubling of the polarization. The term *hyperpolarization* is used to describe the situation when a non-equilibrium

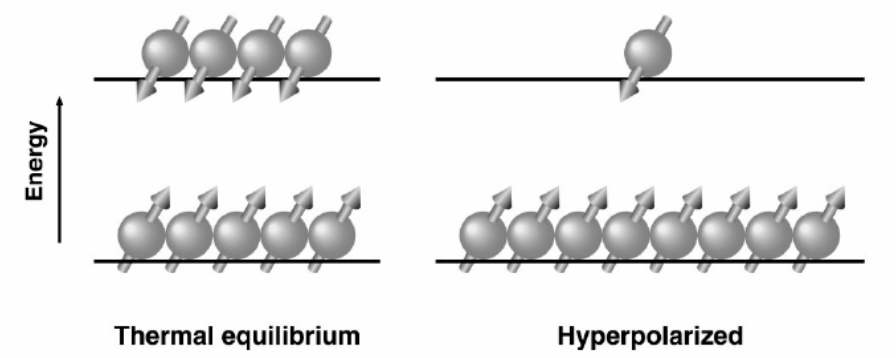

Figure 1. The ordinations of the nuclei at thermal equilibrium and in a hyperpolarized state. The magnetic field is directed vertically downwards.

distribution is created. The population difference between the two states, N^+ and N^-, is altered several orders of magnitude and the magnitude of the polarization may be as high as 0.5! Figure 1 illustrates this situation.
A device used for creating the hyperpolarized state for an imaging agent is called a "polarizer". For the noble gases ^{3}He and ^{129}Xe devices, based on optical pumping using a laser source have been demonstrated by several research groups (1,2). Two different approaches have been presented for hyperpolarization of ^{13}C containing organic molecules: parahydrogen-induced hyperpolarization, PHIP, (3) and DNP hyperpolarization (4). The ^{13}C-methods results in a hyperpolarized liquid that may be injected. While the DNP is a general method and may be applied to a wide range of molecules the PHIP method puts structural limitation on the molecules to be hyperpolarized. The following will concentrate on applications and the results obtained using different types of hyperpolarized ^{13}C containing molecules.

Hyperpolarized imaging agents vs. paramagnetic contrast media
A "traditional" paramagnetic contrast medium operates by altering the relaxation times of surrounding tissues. That is, the signal is generated not by the injected substance, but by the hydrogen nuclei in the water molecules. A hyperpolarized imaging agent will, during an imaging experiment, be the source of the detected NMR signal. The concentration of protons in blood is ~80 M. The ^{13}C concentration in the injected hyperpolarized solution will be in the order of 0.5 M resulting, after dilution due to cardiac output and passage of the lungs, in a concentration in the order of ~10 mM. This in combination with *in viv*o relaxation T1/T2 ~ 45 s / 5 s puts demands on the imaging protocols to be used. However, it should be noted that even after one T1, the available signal in the vascular system will be at least a factor of 2 higher than the one found at 3 T. Another important aspect of a hyperpolarized imaging agent is the total lack of background signal. The signal from the thermal equilibrium polarized nuclei, present in the object, is far below the detection limit. Consequently, only the injected ^{13}C nuclei will contribute to the final image. This is demonstrated in figure 2. The scanner system needs to be equipped with coils and a transmit/receive system capable of operating at the NMR frequency of carbon. Preferable it should allow the

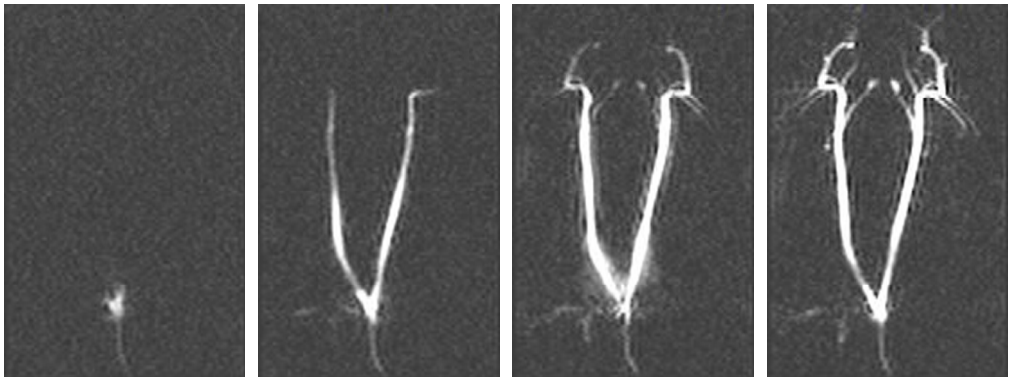

Figure 2. A series of angiograms depicting the head of a pig. The images were acquired during an intra arterial injection of PHIP substance

operator to switch from the carbon frequency to the proton frequency and back, during the image session. This will make it possible to do all preparation scans using proton imaging.
The long T2 relaxation time of hyperpolarized ^{13}C molecules makes it possible to use single-shot sequences based on balanced SSFP, RARE or EPI when imaging the vascular system. This type of sequences converts the initial longitudinal

magnetization to transversal magnetization with almost 100% efficiency. However, in order to image the metabolites following an injection of a biological active hyperpolarized ^{13}C molecule sequences capable of separating substances with peaks at different chemical shift frequencies need to be used.

Clinical applications using hyperpolarized ^{13}C

The possible clinical applications of hyperpolarized ^{13}C compounds may be grouped according to

- Vascular/angiographic imaging
- Perfusion mapping
- Interventional applications
- Metabolic/molecular imaging

Vascular/angiographic imaging

The possibility of real-time vascular imaging using hyperpolarized ^{13}C has been demonstrated (5). Due to the low γ of carbon (only one quarter of the proton value) this type of imaging demands high gradient slew rate and amplitude. However, the total lack of background signal makes it possible to use projection imaging strategies. In the image series shown in figure 2 this has been utilized. The applied imaging sequence, a fully balanced SSFP sequence, uses no slice selection gradient.

Perfusion mapping

The signal obtained from the injected hyperpolarized substance is, after correction for relaxation, direct proportional to the concentration in a specific organ. Consequently, a ^{13}C image, obtained directly after an injection, is a qualitative map of the perfusion. By obtaining a series of images during a bolus injection of a hyperpolarized ^{13}C substance quantitative perfusion maps may be reconstructed (6,7). Figure 3 a-i demonstrates a time series obtained during the passage of hyperpolarized ^{13}C bolus through the heart of a pig. In fig 3j the calculated quantitative perfusion map, superimposed on the corresponding proton slice, is shown.

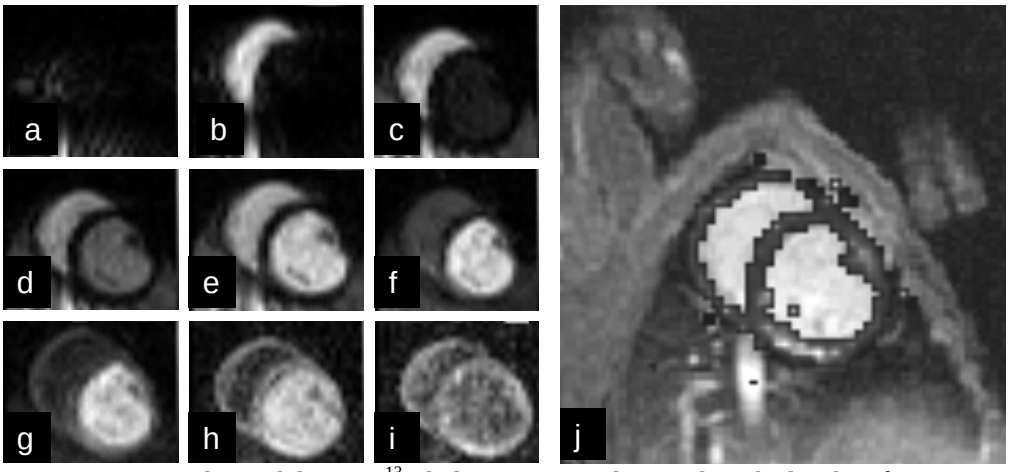

Figure 3. a-i images obtained during a ^{13}C bolus passage and in j is the calculated perfusion map superimposed on a proton slice.

Interventional applications

During an interventional procedure, hyperpolarized ^{13}C may be used in several applications. The vessels may be demonstrated using intra arterial injections and when the catheter is placed in the target organ the perfusion may be mapped. However, the visualization of the catheter itself may also be done using a hyperpolarized ^{13}C substance. Figure 4 shows the results from a catheter tracking experiment. A commercial three lumen catheter was modified in order for two of the lumens to form a loop where the hyperpolarized ^{13}C contrast agent could flow without leaving the catheter. Projection images of the catheter have been superimposed on proton road map images.

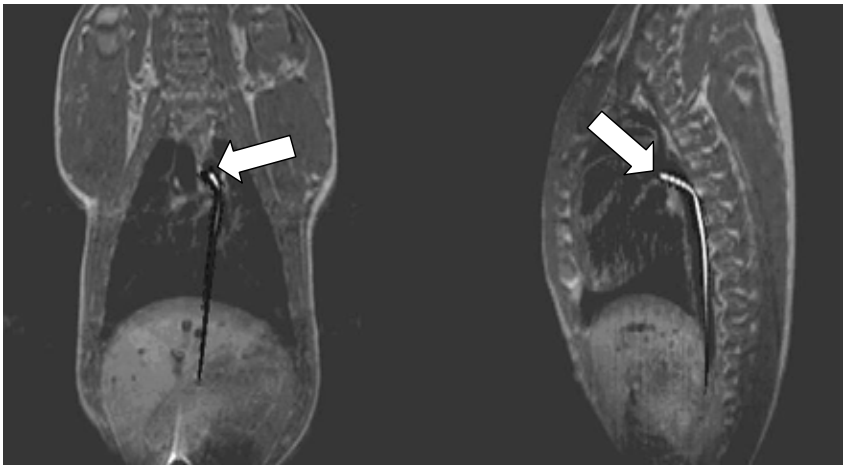

Figure 4. ^{13}C catheter tracking images superimposed on proton roadmaps. The tip of the catheter is indicated by the arrows.

Metabolic/molecular imaging

Since hyperpolarized ^{13}C MR imaging directly informs about the molecule, to which the hyperpolarized atoms are attached, investigation of tissue and cell viability (direct molecular imaging) is feasible. While SPECT and PET only visualizes the distribution of the active nuclei, regardless if they are still contained within the injected molecule or not, NMR is capable of distinguishing signals from the tracer in different molecules (8,9). This is done by obtaining spectral information, through chemical shift imaging (CSI), and reconstructing maps showing the signal from specific molecules. Figure 5a show proton image depicting an implanted colon carcinoma (the arrow) located on the back of a rat and figure 5b shows the molecular map visualizing the lactate

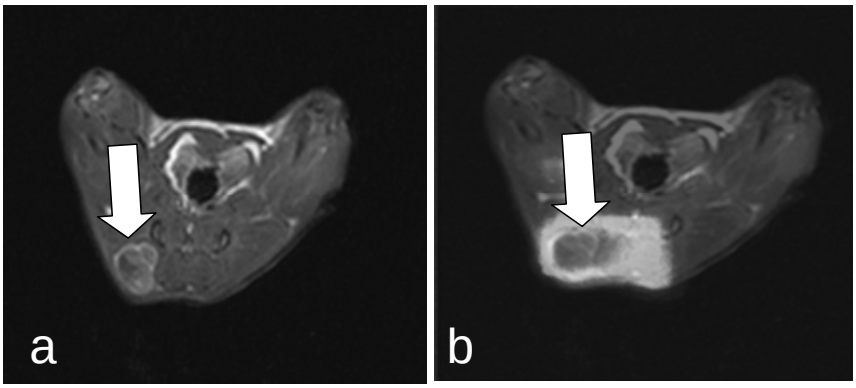

Figure 5. A proton image depicting an implanted colon carcinoma and the corresponding lactate map obtained after injection of hyperpolarized ^{13}C pyruvate

distribution after i.v. injection of a hyperpolarized ^{13}C pyruvate bolus. The lactate map has been superimposed on a proton image. The high metabolic rate in the tumor tissue is clearly demonstrated.

In summary, hyperpolarized ^{13}C imaging may be used to enhance several MR applications. However, the technique is in its infancy. Improvements with respect to SNR due to development of dedicated scanner hardware and software are to be expected.

REFERENCES

1. Albert MS, Cates GD, Driehuys B, Happer W, Saam B, Springer CS Jr, et al. Biological magnetic resonance imaging using laser-polarized ^{129}Xe. Nature 1994; 370:199-201.
2. Middleton H, Black RD, Saam B, Cates GD, Cofer GP, Guenther R, et al. MR imaging with hyperpolarized ^{3}He gas. Magn Reson Med 1995; 33:271-275.
3. Golman K, Axelsson O, Johannesson H, Mansson S, Olofsson C, Petersson JS. Parahydrogen-induced polarization in imaging: subsecond ^{13}C angiography. Magn Reson Med 2001; 46:1-5.
4. Ardenkjaer-Larsen JH, Fridlund B, Gram A, Hansson G, Hansson L, Lerche MH, et al. Increase in signal-to-noise ratio of > 10,000 times in liquid-state NMR. Proc Natl Acad Sci USA 2003;100:10158-63
5. Svensson J, Månsson S, Johansson E, Petersson JS, Olsson LE. Hyperpolarized ^{13}C MR angiography using trueFISP. Magn Reson Med 2003; 50:256-262.
6. Johansson E, Olsson L.E, Månsson S, Petersson J.S, Golman K, Ståhlberg F, Wirenstam R. Perfusion Assessment With Bolus Differentiation: A Technique Applicable to Hyperpolarized Tracers, Magn Reson Med, 2004;52:1043-1051
7. Johansson E, Månsson S, Wirenstam R, Svensson J, Petersson J.S, Golman K, Ståhlberg F. Cerebral Perfusion Assessment by Bolus Tracking Using Hyperpolarized ^{13}C, Magn Reson Med 2004; 51:464-472
8. Månsson S, Johansson E, Magnusson P, Chai CM, Hansson G, Petersson J.S, Ståhlberg F, Golman. ^{13}C imaging – a new diagnostic platform, Eur Radiol 2005;14
9. Golman K, Ardenkjær-Larsen J. H, Petersson J. S, Månsson S, Leunbach I. Molecular imaging with endogenous substances, Proc Natl Acad Sci USA. 2003; 100:10435-10439